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ORIGINAL PAPER

Open-label uncontrolled pilot study to evaluate complementary therapy with *Ruta graveolens* 9c in patients with advanced cancer

Gilles Freyer[1,*], Benoit You[2], Stéphanie Villet[3], Sophie Tartas[2], Cécile Fournel-Federico[2], Véronique Trillet-Lenoir[2], Salima Hamizi[2], Olivier Colomban[2], Nathalie Chavernoz[2] and Claire Falandry[2]

[1]*Université de Lyon, Hospices Civils de Lyon, Service d'Oncologie Médicale, CH Lyon-Sud, Pierre-Bénite, France*
[2]*Centre d'Investigation des Therapeutiques en Onco-hématologie des HCL (CITOH – phase 1 – INCA), Unité de Coordination Onco-gériatrique de Lyon, Service d'Oncologie Médicale, CH Lyon-Sud, France*
[3]*BOIRON, 2 avenue de l'ouest lyonnais, 69510 Messimy, France*

Background: **Patients with advanced metastatic disease are often treated aggressively with multiple lines of chemotherapy, even in the last month of life. The benefit of such an approach remains uncertain. The objective of the study was to investigate whether *Ruta graveolens* 9c homeopathic medicine can improve quality of life (QoL) and tumour progression in patients with advanced cancer.**
Material and methods: **This was a single-centre, open-label, uncontrolled, pilot study. Patients (>18-years, life-expectancy ≥3 months, performance status ≤2) with locally-advanced solid tumours or metastases, previously treated with all available standard anti-cancer treatments were recruited. Oral treatment consisted of two 1-mL ampoules of *Ruta graveolens* (9c dilution) given daily for a minimum of 8 weeks, or until tumour and/or clinical progression. Primary outcome was QoL measured using the EORTC QLQ-C30 questionnaire. Secondary outcome measures were anxiety/depression measured using the Hospital Anxiety and Depression Scale (HADS), WHO performance status (PS), tumour progression assessed using RECIST criteria and tumour markers, survival and tolerance.**
Results: **Thirty-one patients were included (mean age: 64.3 years). Mean duration of treatment was 3.3 months (median: 2.1). QoL global health status improved significantly between baseline and week 8 ($P < 0.001$) and week 16 ($P = 0.035$), but was at the limit of significance ($P = 0.057$) at the end of the study. There was no significant change in anxiety/depression or PS during treatment. *Ruta graveolens* 9c had no obvious effect on tumour progression. Median survival was 6.7 months [95%CI: 4.8–14.9]. *Ruta graveolens* 9c was well-tolerated.**
Conclusion: **Some patients treated with *Ruta graveolens* 9c had a transitory improvement in QoL, but the effectiveness of this treatment remains to be confirmed in further studies.** *Homeopathy* (2014) **103**, 232–238.

Keywords: Pilot study; *Ruta graveolens* 9c; Advanced cancer; Treatment failure; Quality of life; Best supportive care

*Correspondence: Gilles Freyer, Université de Lyon, Hospices Civils de Lyon, Service d'Oncologie Médicale, CH Lyon-Sud, Pierre-Bénite, France.
E-mail: gilles.freyer@univ-lyon1.fr
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Introduction

The management of cancer has improved considerably over the past decade. Thanks to therapeutic advances, survival rates have increased in patients with advanced metastatic disease.[1–3] For these patients, symptom control and optimisation, and enhanced quality of life (QoL) are the primary treatment goals. However, patients with metastatic disease are often treated aggressively with multiple lines of chemotherapy, even in the last month of life.[4] The benefit of such an approach remains uncertain, and it is recognised that the level and duration of disease control decrease with each successive treatment.[5,6] In addition, treatment-related toxicity has an adverse effect on the QoL of cancer patients at the end of their life.

A recent European study in patients with different types of cancer reported that up to one-third of patients use complementary and alternative medicines (CAM) after a diagnosis of cancer.[7] A similar level of use was reported in the UK.[8] A recent Canadian study reported high usage of CAM by women with breast cancer, with as many as 80% using complementary therapies.[9]

Among the different types of CAM available, studies in Western Europe show that a large proportion of patients (42–60%) use homeopathy.[7,10,11] A number of studies have suggested that some homeopathic medicines may help prevent the side-effects of conventional therapies, such as radiodermatitis caused by radiotherapy,[12–14] and nausea and stomatitis associated with chemotherapy.[12,15,16] An observational UK study reported significantly improved QoL, assessed using the EORTC QLQ-C30 questionnaire, in 59% of cancer patients treated with homeopathy, and 63% of these patients also had reduced anxiety–depression (measured using the Hospital Anxiety and Depression Scale: HADS).[17] In parallel, a French study, involving 244 patients with cancer, reported an improved general state in 97% of patients taking CAM (60% used homeopathy).[11] Rostock et al. also reported significant improvement in QoL in cancer patients who used homeopathy for 3 and 12 months, although they failed to find any change in the level of anxiety or depression.[18]

Ruta graveolens is a medicinal plant that contains rutin as its main active component. In complementary medicine, it has been used historically to treat a variety of inflammatory conditions. Its use as an agent with potential anti-tumour activity has been investigated in several *in vitro* and *in vivo* studies in which *Ruta graveolens* has been studied either as an extract or as homeopathic dilutions.[19–23] In these studies, *Ruta graveolens* extract has been shown to have cytotoxic and antiproliferative activity towards a range of human and animal cancer-cell lines, and to delay tumour progression and increase survival times in mouse *in vivo* models.[19,23] At homeopathic dilutions, ranging from 6 to 200c, *Ruta graveolens* showed *in vitro* cytotoxic activity when taken alone[20,21] or when combined with *Calcarea phosphorica* (phosphate of lime)[22]; it has also reduced tumour progression in tumour-xenografted mice.[19] Furthermore, although clinical data are limited, complete tumour regression was reported in six out of seven glioma patients treated with *Ruta graveolens* 6c plus *Calcarea phosphorica* 3c.[22]

However, although most studies suggest that *Ruta graveolens* has a potential benefit, the levels of evidence remain low. No randomised trial, to date, has shown clear improvement in cancer symptoms and/or treatment toxicity.

In view of these preclinical data for *Ruta graveolens* and the previously reported benefits of CAM on the QoL of cancer patients, we carried out a pilot study to investigate whether homeopathic treatment with *Ruta graveolens* 9c increased the QoL of patients with advanced cancer and in whom all conventional anti-cancer treatments had failed. Our secondary objectives were to measure the evolution of anxiety–depression, performance status, tumour response, global survival, progression-free survival and tolerance.

Material and methods

Conduct of the study

This uncontrolled, pilot study was carried out between May 2010 and September 2011 in the Medical Oncology Department of Lyon University Hospital, France. The study was approved by a regional ethics committee (Comité de Protection des Personnes SUD-EST IV) and the AFSSaPS (Agence Française de Sécurité Sanitaire des Produits de Santé; ref: A100078-41). The study was conducted in accordance with the Declaration of Helsinki and in compliance with the International Conference on Harmonization-Good Clinical Practice (ICH-GCP) guidelines and with local enforcement laws (Law n°: 2004-800 of 6th August 2004, and Law n°: 2004-806 of 9th August 2004). All patients provided documented informed consent before their participation in the study and treatment.

Study participants

In this pilot study, it was planned to include a total of 30 patients with pathologically confirmed locally advanced or metastatic solid cancers, in whom, all standard therapies had failed.

Inclusion criteria were being aged >18 years; a life expectancy of ≥3 months; a WHO performance status (PS) of ≤2; histologically proven and a locally advanced solid tumour, not accessible to loco-regional curative treatment, or metastatic cancer; a measurable lesion according to RECIST criteria[24]; progressive disease at inclusion (i.e. increased size of tumour lesions on imagery, and/or an increased tumour marker previously correlated with tumour mass, and/or the deteriorating clinical state of the patient); radiological/imaging that evaluated tumour progression in the previous month; measurement of tumour markers in the previous 2 weeks; patient capable of participating in the treatment follow-up; and a recognised method of contraception during the study period.

Exclusion criteria included receiving an anti-cancer treatment within the previous month or planned during the study period; uncontrolled cerebral metastases or carcinomatous meningitis; concomitant treatment with immunosuppressants (for instance corticosteroids) for >1

week; concomitant treatment with other alternative therapies; participation in another clinical trial (except for an observational study); patient of childbearing age and not using approved contraception; a patient pregnant or breastfeeding; or a serious psychiatric illness.

Study treatment

The study consisted of giving *Ruta graveolens*, at 9c dilution: this is a registered homeopathic medicine in France, prepared by Boiron Laboratories according to European Pharmacopoeia standards, and provided in 1-mL ampoules. Oral treatment was started on day 1 (baseline) at a dose of two ampoules/day: one in the morning and one in the evening, and taken for a minimum of 8 weeks. All patients continued treatment until there was tumour (RECIST) and/or clinical progression, which was defined as the end of study (EOS) (Figure 1).

Data collected

To document the status of pre-baseline disease progression, according to RECIST criteria,[24] all patients had undergone appropriate radiological/imaging and measurement of serum tumour markers within the previous month. The sociodemographic characteristics of the study population were recorded at baseline (day 1). The study's protocol and timeline for collection of data are summarised in Figure 1.

The following data were collected on day 1 and at week 8, and also at weeks 16, 28, 40 and 52 from patients where treatment was continued beyond week 8. (i) QoL was assessed using the EORTC QLQ-C30 questionnaire, which includes five functional scales, three symptomatic scales, six single scales, and the HRQOL-scale. (ii) Anxiety and depression were measured using the HADS, which provides a global score of emotional wellbeing and has anxiety and depressive sub-elements. (iii) Patient autonomy was measured using WHO PS. (iv) Tumour response was assessed by imagery (radiography, CAT scans or MRI) using RECIST 1.1 criteria[24] and defined as a complete response, a partial response, stable disease, or as progressive disease, or assessed by measuring tumour markers (CA15-3, ACE, CA19-9, CA125, PSA and NSE).[21] If disease progression was detected at any point, the patient was informed and it was suggested he stops homeopathic treatment. Alternative management was started, as decided by the patient and the oncologist in charge.

Physical examination, haematological investigations and assessment of tumour markers were carried out on day 1, at week 4, and then at regular 4-weekly intervals thereafter until the EOS.

Primary evaluation criterion

The primary objective of our study was to measure the evolution of QoL during treatment and at the EOS using the EORTC QLQ-C30 auto-questionnaire.

Secondary evaluation criteria

The secondary objectives were to measure: (i) the evolution of anxiety−depression (HADS); (ii) the evolution of PS; (iii) tumour response; (iv) global survival (number of weeks/months between inclusion in the study and death of the patient); (v) survival without disease progression; and (vi) tolerance to *Ruta graveolens* 9c.

Tolerance

All adverse events (AEs) and serious AEs that occurred during the study were recorded and evaluated using National Cancer Institute criteria (version 4). Their relationship to study treatment was assessed.

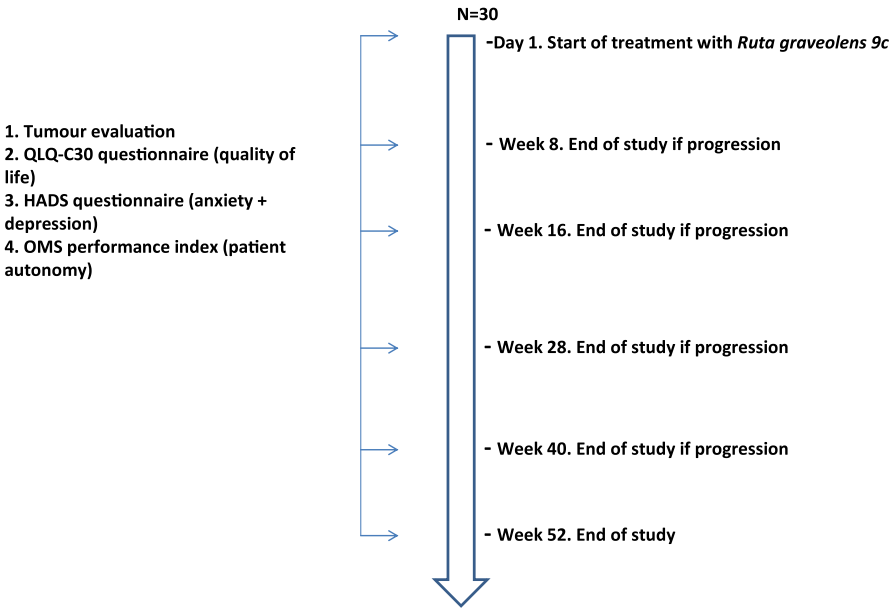

Figure 1 Study protocol.

Statistical analyses

Continuous variables are expressed as their mean, median, standard deviation (SD), or minimum and maximum. Discrete variables are expressed as group size, percentage and 95% confidence intervals (95%CI). The evolution of variables measured at repeated intervals is represented as means ± SD and percentages. The two global criteria, QoL and anxiety−depression, were compared using the non-parametric Wilcoxon's test. Comparisons were carried out between day 1 and the EOS, and between day 1 and weeks 8 and 16. If there were missing data, analysis took into account the last evaluation available according to the last-observation-carried-forward (LOCF) method. Continuous variables were compared with Wilcoxon's test and discrete variables with the chi^2 test. The chi^2 test was also used to compare the evolution of RECIST criteria. All tests were performed with an alpha-risk fixed at 5%, with the level of statistical significance set at $P < 0.05$. All statistical analyses were carried out using R2.14 software.

Results

Description of the study population at baseline

A total of 31 patients (7 males, 24 females) with a mean age of 64.3 years (range: 44−87 years) were included in the study. The baseline characteristics of these patients are summarised in Table 1. Advanced or treatment-refractory breast cancer was the most common type of tumour (29%), followed by renal cancer (16%) and ovarian cancer (13%). As determined by pre-study and baseline tumour data, assessed using RECIST criteria: 64.5% of patients had morphological progression, and 35.5% had morphological stability at inclusion but had increased tumour markers and/or disease-related symptoms. Most patients maintained normal or almost normal activity according to their PS (80.6% had PS ≤ 1). The mean score for QoL at inclusion was 43.6 (range: 0−66.7) and the mean score for anxiety−depression (HADS) was 17.7 (range: 6−29) (Table 1). Twenty-one patients (70%) had a HADS score of ≥15, indicating emotional disturbance. For the HADS anxiety−depression subscores, if 'uncertain' was included as an affirmative response for assessment of anxiety/depression, 70% of patients were anxious and 63% were depressed (Table 1).

Table 1 Baseline characteristics of the study population

Characteristics at inclusion (n = *31)*	*Mean [range] or* n *(%)*
Age (years)	64.3 [44−87]
Weight (kg)	62.3 [44−116]
Tumour type	
Breast	9 (29%)
Kidney	5 (16%)
Ovary	4 (13%)
Colo-rectal	3 (10%)
Lung	2 (6%)
Prostate	2 (6%)
Pancreas	1 (3%)
Stomach	1 (3%)
Endometrium	1 (3%)
Peritoneum	1 (3%)
Appendix	1 (3%)
Quality of life [0−100], (n = 30)	43.6 [0−66.7]
HADS (n = 30)	
Global score [0−42]	17.7 [6−29]
Normal state	9 (30%)
Emotional unbalance	21 (70%)
Anxiety sub-score [0−21]	9.1
Certain [>10]	10 (33.3%)
Uncertain [8−10]	11 (36.7%)
Normal [<8]	9 (30%)
Depression sub-score [0−21]	8.5
Certain [>10]	8 (26.6%)
Uncertain [8−10]	11 (36.7%)
Normal [<8]	11 (36.7%)
Performance status (PS) (n = 31)	
0	6 (19.3%)
1	19 (61.3%)
2	6 (19.4%)
Morphological status (n = 31)*	
Stable	11 (35.5%)
Progressive	20 (64.5%)

* Morphological status at baseline was established using RECIST criteria. Patients with morphological stability assessed by imagery at baseline also had a tumour marker increase and/or disease-related symptoms increase.

Primary evaluation criterion

QoL: Twenty-four of the 31 patients (77.4%) were included in the final analysis of QoL. One patient was excluded as he did not complete any of the questionnaires and six were excluded as they only completed one questionnaire. In these patients, early symptomatic progression of the tumour led to the EOS. For the 24 patients analysed, EORTC QLQ-C30 scores were available from baseline until week 8, with data for week 16 available for nine patients. When QoL status was compared between baseline and week 8 the difference was statistically significant ($P < 0.001$) (Table 2). For patients with QoL measured at week 16, a significant improvement was also found ($P = 0.035$). Furthermore, in each case, the mean improvement from baseline was >10 points, which translates into a meaningful clinical improvement.[25] For the whole study cohort, there was a trend towards improved QoL (global health status) from inclusion until the EOS, although this was not statistically significant ($P = 0.057$).

Secondary evaluation criteria

Anxiety/depression: There was no significant difference in the HADS global score or subscores for anxiety−depression between inclusion and weeks 8, 16 and the EOS (data not shown).

Index of performance status: There was no significant change in PS during treatment (Table 3). At week 8, three patients had improved PS while receiving *Ruta graveolens* 9c, and a similar number after 16 weeks of treatment. However, the majority of patients had no change or deterioration in PS during the study.

Tumour response: For the complete patient cohort, treatment with *Ruta graveolens* 9c had no significant effect on tumour response, assessed using RECIST criteria and by measuring tumour markers. As part of our planned analyses, responses in patients were stratified according to their morphological status at baseline (i.e. whether they showed morphological stability or progression compared

Table 2 Evolution of quality of life (QoL) score (global health status) with *Ruta graveolens* 9c treatment

Assessment	*Baseline (n = 24)*	*Week 8 (n = 24)*	*Week 16 (n = 9)*	*End of study (n = 24)*
QL2 score Mean [SE]	42 [16.9]	55.2 [18.5] $P < 0.001$*	55.6 [22.2] $P = 0.035$*	49.6 [21.4] $P = 0.057$

* Significant using the Wilcoxon test.

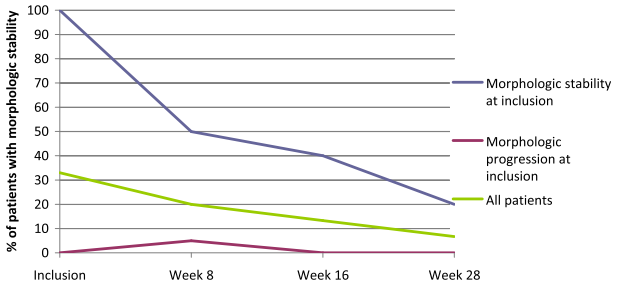

Figure 2 Presence of morphologic stability (tumour response) assessed by imagery (RECIST criteria) up to week 28 in three groups of patients: those with morphologic stability at inclusion (n = 10), those with morphologic progression at inclusion (n = 20) and all patients (n = 30).

to pre-study evaluations). Of the 10 patients who showed morphological stability assessed by imagery at baseline, 50% were stable after 8 weeks of treatment, 40% at week 16 and 20% at week 28 (Figure 2). Of the 20 patients with morphological progression, assessed by imagery at baseline, only one (5%) remained stable after 8 weeks of treatment (Figure 2). The mean duration of morphologic stability was 5.3 months.

Overall survival and survival without disease progression: Median overall survival was 6.7 months [95%CI: 4.8−14.9], median progression-free survival (clinical, biological or RECIST criteria) was 1.9 months [95%CI: 1.8−2.2] and median survival without any deterioration in QoL (additional cancer treatment, and/or hospitalisation, and/or 20% decrease in QoL score) was 2.2 months [95%CI: 2.0−3.9].

Tolerance: Mean duration of treatment was 3.3 months (median: 2.1; range: 0.4−11), during which *Ruta graveolens* 9c was well-tolerated. A total of 257 AEs were reported in the 31 patients (Table 4). Twenty-eight patients (90%) had at least one AE, with an average of nine AEs per patient. The most frequent AEs reported during the study were abdominal pain (10.9%), fatigue (10.5%), musculoskeletal pain (10.5%) and headaches (4.7%). Seven serious AEs were also reported, all related to the disease. None of the AEs or serious AEs was considered to be directly related to treatment with *Ruta graveolens* 9c.

Discussion

This is the first study in Europe to report the usage of a homeopathic medicine given to a well-described cohort of patients with end-stage cancer. Our data suggest that patients treated with *Ruta graveolens* 9c experienced significant and clinically meaningful improvements in QoL after 8 weeks of use, which was sustained over 16 weeks of treatment (Table 2). However, no significant improvements in secondary QoL assessments (HADS) were observed, and improvements in PS during treatment were seen in only a few patients (Table 3).

Table 3 Evolution of performance status (PS) during *Ruta graveolens* 9c treatment

PS change from baseline (n = 31)	*Week 8 (n = 25)*	*Week 16 (n = 9)*	*End of study (n = 29)*
Improvement	3 (12%)	3 (33%)	2 (7%)
No change	13 (52%)	3 (33%)	11 (38%)
Deterioration	9 (36%)	3 (33%)	16 (55%)

Taken as a whole, these results support those of previous authors who have shown that homeopathic treatment can improve QoL or general state in cancer patients.[11,17,18] However, in concordance with the report of Frenkel,[26] we found no specific anti-tumour effects from this homeopathic medicine, despite the promising profile of *Ruta graveolens in vitro* and in experimental animals.[19−23]

There are three approaches to the treatment of patients with end-stage cancer: palliative chemotherapy, aimed at improving symptoms and postponing future symptom development; palliative radiotherapy; or best supportive care, aimed at improving or maintaining QoL. The patient's choice of therapeutic approach is strongly influenced by their inner perceptions of treatment, even before discussing it with their oncologist.[27] Many studies show that end-stage cancer patients are ready to accept the major toxicities associated with chemotherapy for only small therapeutic benefits,[27−29] although the minimum survival benefit after accepting toxic chemotherapy varies extensively from one patient to another.[30] Treatment refusal and the initiation of best supportive care may, however, be beneficial to some patients

Table 4 Treatment-emergent adverse events (AEs) occurring in the study population (n = 31)

Most common adverse event		n *(%)*
Abdominal pain		28 (10.9)
Fatigue		27 (10.5)
Musculoskeletal pain		27 (10.5)
Headache		12 (4.7)
Dyspnoea		9 (3.5)
Loss of appetite		8 (3.1)
Diarrhoea		7 (2.7)
Nausea		7 (2.7)
Constipation		6 (2.3)
AE ≥ grade 3	*Event (n; grade)*	*Patients (n)*
Bowel obstruction	2; grade 3	2
Cholestasis	2; grade 3	1
Cytolysis	2; grade 3	1
Dysphagia	1; grade 3	1
Dyspnoea	1; grade 3	1
Constipation	1; grade 3	1
Malnutrition	1; grade 3	1
Abdominal pain	1; grade 3	1
Musculoskeletal pain	1; grade 3	1

and could avoid the temptation of undertaking yet another line of futile and toxic chemotherapy.

Several hypotheses can be proposed to explain the improved QoL reported by our patients. First, a placebo effect cannot be discounted. However, in a review of randomised placebo-controlled trials in cancer patients, Chvetzoff and Tannock reported that there was limited improvement in patients receiving a placebo and that placebo effects on QoL and PS were relatively rare.[31] Thus, the significant improvement in QoL seen in our patients seems unlikely to be due to a placebo effect.

The second hypothesis is that improved QoL was caused by the specific management and attention paid to the patients during this study. We feel that this is unlikely as, throughout this study, patient management within the framework of routine hospital care was unchanged, with no particular extra attention given to the patients under study.

The third hypothesis is that it could be due to changing to best supportive care following cessation of specific cancer therapies. It is well recognised that chemotherapy-related toxicities greatly influence the patients' experience and negatively impact on QoL,[32,33] and that QoL may improve following treatment cessation. We cannot exclude this phenomenon from our study.

The fourth hypothesis is that improvements in QoL could be a result of natural fluctuations in the course of the disease (spontaneous tumour regression).[31] This is unlikely as the majority of patients had morphological progression at baseline, with the best response being short-term stability rather than regression.

Finally, we cannot exclude the possibility that the improved QoL observed with *Ruta graveolens* 9c represented a genuine effect. Indeed, the improvements seen (>10 points improvement in the QoL score) suggest that this is a small, but clinically meaningful outcome. Furthermore, our study's concept and *Ruta graveolens* 9c treatment itself were both received favourably by the patients and the clinicians involved. In part because of the paucity of treatment-related AEs, compliance with treatment was good. Indeed, 20% of patients (5/30) chose to continue *Ruta graveolens* 9c treatment at their own request, despite tumour progression, for a mean period of 6−36 weeks beyond the EOS.

Our study has several limitations. The main limitations are the small population size and the lack of a comparative control group. Furthermore, there was also no control for other medications or for medication changes that could have had a significant impact on QoL. It should be pointed out that this was only a pilot study to test a hypothesis, and that larger randomised, controlled trials are necessary to confirm a benefit of *Ruta graveolens* 9c in this clinical situation.

Conclusion

Patients with metastatic disease are often treated aggressively with multiple lines of toxic chemotherapy, even in the last month of life. *Ruta graveolens* 9c may benefit patients with heavily-pretreated advanced cancer in terms of QoL. However, no significant effect was observed on tumour progression.

In light of our data and the limitations of this pilot study, further studies are planned to evaluate the role of homeopathic treatments in the management of patients with terminal cancer as an alternative to conventional care, when all standard cancer therapies have failed.

Conflict of interest statement

Stéphanie Villet is an employee of Laboratoires Boiron. The other authors declare no competing financial interests.

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